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09/380,337	03/06/2000	SETTARA CHANDRASEKHARAPPA	15280-315100	2491

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	17

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/380,337	Chandrasekharappa
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 24, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-24 and 26-37* is/are pending in the application.

4a) Of the above, claim(s) *9-18, 27-29, 34, and 35* is/are withdrawn from consideration.

5) ☒ Claim(s) *4 and 7* is/are allowed.

6) ☒ Claim(s) *1-3, 5, 6, 8, 19-24, 26, 30-33, 36, and 37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed June 19, 2002 (Paper No. 14) in response to the Office Action of December 19, 2001 (Paper No. 13) is acknowledged and has been entered. Previously pending claim 25 has been canceled, claims 1, 8, 19-20, 24, 26, 36 have been amended. Claims 1-8, 19-24, 26, 30-33, 36-37 are currently being examined.

2. The text of those sections of Title 35, US Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC § 112

4. Claims 19-23 and 31 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 13, Section 4, pages 4-5.

Applicant argues that Webster's 3rd International defines the term "essentially" as meaning "by its very nature" or "fundamentally" and thus the meaning of the claim is clear, especially in light of the further limitation in the claim that the hybridizing oligonucleotide hybridizes to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3. The argument has been considered but has not been found persuasive because neither the claim as amended, nor the specification and claims as originally filed defines the term "essentially" and Webster's 3rd definitions are not limiting. For example, what does fundamentally/by its very nature mean in terms of the claimed nucleotide. Further, the claim does not provide a nexus between "essentially encoding" and 95% identity to SEQ ID NO:3 since SEQ ID NO:3 is the genomic sequence for the MEN1 gene which contains noncoding nucleic acid residues. Applicant's arguments have not been found persuasive and the rejection is maintained.

5. Claim 31 remains rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 13, Section 4, page 5.

Applicant argues that stringent hybridization and wash conditions are defined in the specification and in order to expedite prosecution, the claim has been amended to recite specific hybridization wash conditions. The argument has been considered but has not been found persuasive because claim 31 has not been amended. Applicant's arguments have not been found persuasive and the rejection is maintained.

6. Claims 1-3, 5, 8, 24, 26, 30-33 and 36-37 remain rejected under 35 USC 112, first paragraph and newly amended claims 19-24 and 26 (which now recite a nucleic acid sequence comprising at least 95% of SEQ ID NO:3), are rejected under 35 USC 112, first paragraph for the reasons previously set forth in paper No. 13, Section 6, pages 5-10.

Applicant argues that (a) the requirement under 35 USC 112, first paragraph is easily met by the specification as filed and Applicants have provided the required guidance and working examples to identify the claimed nucleic acids, (b) the molecular weight of the protein encoded by the claimed nucleic acid is a structural feature of the claimed sequence, (c) the protein encoded must specifically bind to specific polyclonal antibodies raised against SEQ ID NO:2 which is an additional structural feature that allows one of skill to identify the claimed genus of nucleic acids, (d) a protein encoded by the nucleic acid must have at least 60% identity to the sequence which is an additional structural feature that allow one of skill to identify the claimed genus of nucleic acids.

The arguments have been considered but have not been found persuasive (a') for the reasons of record, (b') molecular weight is a descriptive but not a structural feature since no particular structure can be defined by the molecular weight, (c') it is notoriously well known in the art that the specificity of antibody binding is determined by the epitope to which the antibody binds. Roitt et al, (Immunology, 1993, Mosby, St. Louis, p 6.4-6.5) specifically teaches that when the determinants of antigen A are shared by another antigen, B, then antibodies that bind to those determinants in A will also react with B. This phenomenon is termed cross-reactivity (see Fig 6.8 on page 6.4 and p. 6.5, para 1), thus any antibody that binds specifically to any epitope of SEQ ID NO:2 will also bind specifically to other proteins that share the same epitope. It is noted that no particular epitope is identified either in the claim or the specification as filed. The claimed specific binding of the antibodies does not identify a the antibodies would "specifically bind" to many different about 67.5 kD proteins, displaying the same epitope, that have neither structural nor functional identity with the protein encoded by the claimed molecule, (d') for the reasons previously set forth drawn to the teachings of Bowie, Burgess, Lazar and Bork.

Applicant further argues that (e) the term "specifically binds" is defined in the specification on page 12, starting at line 24 wherein the specific binding occurs when the specified antibodies bind to a particular protein and do not bind in a significant amount to other proteins present in the sample and is determinative of the presence of the protein in a heterogeneous population of proteins, thus this definition excludes non-specifically binding antibodies that bind to regions common to an innumerable number of proteins, (f) the specification teaches how to perform cross-reactivity

determinations, (g) undue experimentation is not required to identify polypeptides with the specified molecular weight that have at least 60% identity to SEQ ID NO:2.

The argument has been considered but has not been found persuasive because (e') while applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term, In re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947), for the reasons set forth above, specificity of an antibody is understood by those of skill in the art to reside in epitope binding and not in selectivity of a particular protein. It is clear that polyclonal antibodies are not and cannot be selective for a particular protein because they are produced by exposure of the antigen to the immune system of an animal and bind to numerous epitopes on that antigen. Further, the specification recognizes that selectivity for a particular protein, that is binding to one protein but not significantly to other proteins, "may require an antibody that is selected for its specificity for a particular protein". The claimed specific binding of the antibodies does not identify a specific structure of SEQ ID NO:2 that can be used to identify the claimed genus of nucleic acids since it would be expected that the polyclonal antibodies would "specifically bind" to many different about 67.5 kD proteins displaying the same epitope that have neither structural nor functional identity with the protein encoded by the claimed antibody, (f') because the genus is highly variant, the disclosure of specific nucleotide sequences encoding and the ability to screen antibodies, is insufficient to enable the claimed invention, (g') for the reasons previously set forth drawn to the teachings of Bowie, Burgess, Lazar and Bork.

Applicant further argues that one of skill could readily determine any one of the claimed embodiments and although many menin encoding nucleic acid sequences are theoretically possible, one of skill can readily determine one by one, a particular menin encoding sequence without undue experimentation. The argument has been considered but has not been found persuasive because the claims as currently constituted are not drawn to menin encoding nucleic acid sequences but rather to nucleic acid sequences which encode a protein which has a particular molecular weight that binds to an antibody raised against a sequence set forth in SEQ. ID NO:2, has at least 60%, 80% homology to SEQ ID NO:2, hybridizes to SEQ ID NO:1 under unspecified conditions. Examiner clearly states that the specification is enabling for a polynucleotide encoding the protein of SEQ ID NO:2 or a polynucleotide comprising SEQ ID NO:1 or 3 which clearly read on menin encoding nucleic acid sequences. The rejection can be obviated by limiting the claims to a polynucleotide encoding the protein of SEQ ID NO:2 or a polynucleotide comprising SEQ ID NO:1 or 3

New Grounds of Objection

7. The amendment filed June 19, 2002 is objected to under 35 USC 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is the substitution of "formamide" for "formalin with 1 mg heparin" in the paragraph starting on page 13, line 13 and continuing on page 14 through line 11.

Applicant is required to cancel the new matter in the response to this Office action.

Applicant argues that the amendment contains no new matter because the use of formamide in standard hybridization solutions is well known and that since Sambrook, which discloses the general methods of use of the invention, is incorporated by reference - no new matter has been added.

The argument has been considered but has not been found persuasive because nothing in the specification as originally filed is drawn to the newly added amendment. Further, MPEP 6.08.01(p) specifically states that:

"Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky , 474 F.2d 671, 177 USPQ 144, (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.

The objection can be overcome by meeting the requirements of MPEP 6.08.01(p) wherein the MPEP further states that:

"Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins , 486 F. 2d 569, 179 USPQ 157

(CCPA 1973); In re Hawkins , 486 F. 2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins , 486 F. 2d 577, 179 USPQ 167 (CCPA 1973)."

New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. Claims 19-24 and 26 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitations of "specifically hybridizing to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3" and the nexus, suggested by Applicant, between "essentially encoding" and "95% identity to SEQ ID NO:3" has no clear support in the specification and claims as originally filed. Applicant points to support for the newly added limitations at page 10, lines 14-27 and page 14 lines 12-20. A review of the suggested support reveals support for a gene encoding the polypeptide menin and the presence of mutations in MEN1 producing a nonfunctional MEN1 allele (p. 10) and support for the term "substantial identity' being defined as comprising a sequence that has at least 85%, 90 to 95% identity as compared to a reference sequence over a comparison window of at least 20 nucleotide positions wherein the reference sequence may be a subset of a larger sequence (p. 14). The suggested support is not persuasive because there is no nexus between the definition of percent identity on page 14 and an assay for detecting a mutation wherein the first oligonucleotide specifically hybridizes to a nucleic acid comprising at least 95% identity to SEQ ID NO:3. Further, neither the claims nor the specification as originally filed defines a polynucleotide "essentially encoding" human menin as a polynucleotide comprising at least 95% identity to SEQ

ID NO:3. The subject matter claimed in claims 19-24 and 26 broadens the scope of the invention as originally disclosed in the specification.

9. Claims 8 is are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of hybridization conditions containing 50% formamide at 42 degrees centigrade has no clear support in the specification and the claims as originally filed. Applicant points to the newly amended paragraph on page 13, starting at line 13 and bridging to page 14 line 2, for support for the newly amended claim. The argument has been considered but has not been found persuasive for the reasons set forth above, that is, that the newly amended specification is drawn to new matter. The subject matter claimed in claim 8 broadens the scope of the invention as originally disclosed in the specification.

10. Claims 1-3, 5-6, 8, 19-24, 26, 30-33, 36-37 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for SEQ ID NOS 1 and 3, does not reasonably provide enablement for nucleic acid molecules encoding menin/SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to nucleic acid encoding menin, SEQ ID NO:2. This includes a whole universe of degenerate sequences which encode SEQ ID NO:2. The specification teaches SEQ ID NOS 1 and 3, the cDNA and genomic DNA, respectively, which encode SEQ ID NO:2. The specification teaches that SEQ ID NO:3 is mutated in samples from clinically diagnosed patients with multiple endocrine neoplasia type 1 (p. 50) and teaches that the mutations detected in SEQ ID NO:3

would most likely result in loss of function of the protein product which is consistent with a tumor suppressor mechanism (p. 53). One cannot extrapolate the teaching of the specification to the scope of the claims because there is no teaching that any nucleic acid encoding menin other than SEQ ID NO:3 is mutated and will distinguish type1 from type 2 multiple endocrine neoplasia type 1. No function appears to have been ascribed to the claimed nucleic acid other than its ability to distinguish type 1 from type 2. It cannot be predicted, given the information in the specification and known in the art, whether or which other sequences that encode menin/SEQ ID NO:2 will distinguish type 1 from type 2. Applicant is clearly aware of the conventional understanding in the art that different sequences will encode the same protein because on page 10 of Paper No 14, Applicant quotes the Guidelines in that "a listing of all possible DNAs which encode a given protein is a practical impossibility due to the enormous number of such nucleic acids"and states that "although many menin encoding nucleic acid sequences are theoretically possible.....any particular menin sequence" can be determined without undue experimentation. Again, there is no teaching that any nucleic acid other than SEQ ID NO:3 will be mutated and will distinguish type 1 from type 2. The protein, although recombinantly expressed, has not been characterized and therefore no functional use has been established for the protein. There is no teaching that the protein is actually expressed *in vivo,* or that it is differentially expressed in type 1 compared to type 2. This is not sufficient to enable the claimed nucleic acid encoding menin/SEQ ID NO:2 because it is notoriously well known in the art that that expression of mRNA, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular

Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if SEQ ID NO:3 could in fact translated into a polypeptide expression product. Finally, there is no teaching that the protein is differentially expressed in type 1 compared to type 2 or if not, what function it might possess, thus one would not know how to use the encoded protein and by extension, one would not know how to use the nucleic acid encoding the protein if it did not mutate and was unable to distinguish type 1 from type

2. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention

11. All other objections and rejections recited in Paper No. 13 are withdrawn.

12. Claims 4 and 7 are free of the art and appear to be allowable .

13 Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 28, 2002